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(54) **ROSACEA TREATMENTS AND KITS FOR PERFORMING THEM**

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See application file for complete search history.

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(57) **ABSTRACT**

Regimen for the treatment of rosacea include the application of an anti-redness composition to at least a portion of the cleansed area of skin afflicted with rosacea. The regimen may include the application of one or more of a polymetal complex, a composition containing metronidazole, and/or a protective composition. Kits containing components useful in performing such regimens are also described.

7 Claims, No Drawings

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ROSACEA TREATMENTS AND KITS FOR PERFORMING THEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation which claims the benefit of and priority to U.S. patent application Ser. No. 13/144833, filed Jul. 15, 2011 which is a U.S. National Stage Application filed under 35 U.S.C. §371(a) of International Application No. PCT/US2010/021995, which claims the benefit of and priority to U.S. Provisional Application Nos. 61/146,960, filed on Jan. 23, 2009 and 61/225,041 filed on Jul. 13, 2009.

TECHNICAL FIELD

The present disclosure relates to compositions and methods for the treatment of rosacea.

BACKGROUND

Rosacea is a chronic inflammatory disease that occurs primarily in fair skinned people. By some recent estimates rosacea afflicts 13 million Americans. It usually first appears as subtle reddening on the face. Over time this may develop into inflammation, be accompanied by skin eruptions, and in the appearance of red lines which result from swollen or damaged veins and capillary blood vessels immediately under the surface of the skin.

There is no single test to determine whether someone has rosacea. The diagnosis is usually made based on a visual examination and from identifying a number of symptoms, such as: flushing or blushing that occurs easily and often and lasts longer than normal; erythema (i.e., rashes and redness on part or all of the face); burning or stinging sensations; papules, or pustules; rhinophyma; and/or telangiectasis caused as a result of capillary blood vessels in the face becoming enlarged or damaged. Symptoms are often aggravated by sun exposure, changes or extremes in temperature, wind, and consumption of certain foods (including spicy foods, caffeine & alcohol).

Rosacea is generally categorized into four stages. Stage one is characterized by flushing or redness (known as erythema) that lasts for hours or days. Red lines (a condition known as telangiectases) may appear. Stages two and three, Papulopustular and Phymatous, are characterized by skin eruptions (nodules, papules pustules). Symptoms may spread from the face to other parts of the body such as the scalp, neck, and chest. Stage four, Ocular, is characterized by large nodules appearing, severe inflammation, facial pain, swelling, and burning. Rhinophyma the bulbous enlargement of the nose may also be present with some subjects.

The exact cause of rosecea is still largely unknown, however the symptoms are reasonably well understood as are a variety of lifestyle factors (such as particular foods and activities) that are known to trigger outbreaks in people that have the disease. Although there is not yet a cure for rosacea, a combination of treatment of the symptoms and lifestyle changes to avoid these triggers can greatly reduce the negative impacts of rosacea.

In general, the treatment is aimed at the control of redness, inflammation, and skin eruptions. Treatment is necessary to prevent permanent damage and progression of the symptoms. In more severe cases, once a diagnosis of rosacea has been made a dermatologist will prescribed a combination of oral antibiotics and the use of antibiotic gel as initial treatment. The oral antibiotics (e.g., minocycline or erythromycin) will bring the condition under control (reducing redness and the formation of papules and pustules), then the topical treatments will be used to keep the symptoms under control. Since rosacea cannot be cured it is often necessary to continue topical treatment (and modification of lifestyle factors) even after symptoms have been reduced or disappeared. In addition, laser treatments may be employed to seal the broken vessels and prevent blood flow to the surface off the skin. Alternatively, mixed intense pulse light (IPL) may be employed to treat Rosacea symptoms. Light pulse therapy works by sending light energy through the outer skin, concentrating on the dermal layer just below and attacks the problem from the inside, stimulating growth of collagen.

One commercially available treatment for rosacea is Metrogel, from Galderma Laboratories, Fort Worth, Tex. USA. This product is indicated for the topical treatment of inflammatory lesions associated with rosacea and is not clinically approved for reducing redness.

There is thus a continuing need for improved and effectual treatments for rosacea, especially the rapid and effective reduction in redness of the skin associated with rosacea.

SUMMARY

The present disclosure provides a treatment regimen including cleansing at least a portion of an area of skin afflicted with rosacea with a cleanser; applying a composition containing metronidazole to at least a portion of the afflicted area; and applying an anti-redness composition to at least a portion of the cleansed and metronidazole-treated area.

The present disclosure also includes a treatment regimen including cleansing at least a portion of an area of skin afflicted with rosacea with a cleanser; applying a composition containing metronidazole to at least a portion of the afflicted area; applying an anti-redness composition to at least a portion of the afflicted area; and applying a protective composition to at least a portion of the afflicted area.

In another embodiment, the present disclosure provides a kit including an antimicrobial cleanser; a composition containing metronidazole; and an anti-redness composition.

Additionally disclosed is a treatment regimen including cleansing at least a portion of an area of skin afflicted with rosacea with an antimicrobial or cleanser; applying a composition containing a polymetal complex to at least a portion of the cleansed area; and applying a protective composition to at least a portion of the cleansed, and polymetal complex-treated area.

The present disclosure further includes a treatment regimen including cleansing at least a portion of an area of skin afflicted with rosacea with an antimicrobial or cleanser; applying a composition containing a polymetal complex to at least a portion of the cleansed area; and applying a protective composition to at least a portion of the cleansed, and polymetal complex-treated area.

A kit is disclosed in the present disclosure. The kit includes a cleanser; a composition containing a polymetal complex; and a protective composition.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present disclosure describes methods for treating skin afflicted with rosacea which include the sequential applica-

tion of certain products. In embodiments, the disclosure includes sequential application of: a) a cleanser; b) a composition containing metronidazole; c) an anti-redness composition; and, optionally d) a protective composition. In embodiments, the disclosure includes application of a redness-reducing amount of a polymetal complex to at least a portion of the afflicted skin. The polymetal complex may be applied alone, following cleansing and/or in a regimen that also involves the application of a metronidazole-containing composition.

The specific sequence of products applied in accordance with this disclosure will depend on the severity of the rosacea. The present regimens provide better results than any of the individual products used in the regimen and also provide a result that exceeds the sum of the individual results provided by the individual products.

The Cleanser

The cleanser can be any non-soap cleanser that will remove dirt and oil from the skin. Suitable cleansers are commercially available and typically include a combination of anionic, cationic, amphoteric and/or non-ionic surfactants in an aqueous vehicle. The cleanser advantageously can include a combination of compounds to compensate for the well known fact that cleansing agents, by their very nature, are not always well tolerated by the skin. The oil-removal feature of a cleanser can result in drying of the skin, and even skin irritation. By incorporating various protective agents in the cleanser process the preferred cleanser overcomes shortcomings found in many alternative products. Thus, in one particularly useful embodiment the cleanser is a foaming gel cleanser that contains water, sodium lauroyl oat amino acids, cocamidopropyl betaine, sodium laureth sulfate, aloe barbadensis leaf juice, medicago sative (alfalfa) extract, borago officinalis extract, chamomilla recutita (matricaria) extract, sodium chloride, xanthan gum, saponins, phenoxyethanol, methylparaben, propylparaben, ethylparaben, butylparaben, fragrance, and color. In embodiments, the cleanser frees the skin of pollutants without damaging the skin's own natural moisture content. It also leaves all skin types clean and extremely soft to the touch.

In embodiments, in addition to removing dirt and oil from the skin, the cleanser also reduces the skin bacterial count. Such antimicrobial or antibiotic cleanser may include an antimicrobial or antibiotic compound. The antimicrobial or antibiotic compounds employed in the cleanser are not particularly limited. Examples of such antimicrobial or antibiotic compounds include, but are not limited to: chlo ohexidine gluconate, quaternary ammonia type compounds, alcohol based cleansers (ethanol, isopropyl alcohol, etc.), triclosan, zinc pyrithione, sodium sulphacetamide, clindamycin phosphate, and the like. It is envisioned that one or more antimicrobial agents may be used.

In embodiments, one suitable foaming gel cleanser contains a combination of water, cocamidopropyl betaine, sodium lauroyl oat amino acids, sodium laureth sulfate, glycerin, aloe barbadensis gel, glycerth-7, apricot triethanolamine, sage extract, borage extract, phenoxythanol, methylparaben, propylparaben, ethylparaben, butylparaben, saponins, fragrance, and colorant.

The Composition Containing Metronidazole

In embodiments, a composition containing metronidazole is applied to the cleansed skin of the person afflicted with rosacea.

Metronidazole is a nitroimidazole used in the treatment of infections caused by susceptible organisms, particularly anaerobic bacteria and protozoa. Metronidazole is a prodrug. It is converted in anaerobic organisms by the redox enzyme pyruvate-ferredoxin oxidoreductase. The nitro group of metronidazole is chemically reduced by ferredoxin (or a ferredoxin-linked metabolic process) and the products are responsible for disrupting the DNA helical structure, thus inhibiting nucleic acid synthesis. Metronidazole is selectively taken up by anaerobic bacteria and sensitive protozoal organisms because of the ability of these organisms to reduce metronidazole to its active form intracellularly.

The composition containing metronidazole can be formulated in any manner to provide delivery of the active to the skin of a patient afflicted with rosacea. In embodiments, the composition containing metronidazole contains from about 0.001 to about 5 percent metronidazole by weight of the composition, in embodiments from about 0.1 to about 3 percent metronidazole by weight of the composition, in other embodiments from about 0.5 to about 1.5 percent metronidazole by weight of the composition.

Metronidazole is commercially available as a gel preparation for the treatment of dermatological conditions such as rosacea. Illustrative commercially available compositions containing metronidazole are available under the tradename METROGEL® from Galderma Laboratories, Fort Worth, Tex. USA. In fact, METROGEL is available from Galderma Laboratories in a kit with a gentle skin cleanser commercially available under the tradename CETAPHIL®.

Anti-Redness Composition

Optionally, an anti-redness composition may be applied. The anti-redness composition is a composition containing one or more ingredients that result in redness reduction of the skin, either via a clinical and/or visual manner. The anti-redness composition may include botanicals, calming agents, anti-microbial agents, anti-inflammatory compounds, anti-oxidants, antiseptics, conditioning agents, light refracting materials and the like. Non-limiting examples of such ingredients include Aloe Barbadensis Leaf juice, Hydrolyzed Oat Protein, Bisabolol, Allantoin, Avena Sativa (Oat) Beta Glucan, Avena Sativa (Oat), Kernel Extract, Glycyrrhiza Glabra root extract, Sea Whip Extract, Mica, Titanium Dioxide, Iron Oxides, Bacopa Monniera Extract, Arnica Montana (Flower) Extract, Cupressus Sempervirens (Seed) Extract, Polygontum Multiflorum Extract, Sodium Cocoyl Amino Acid, Sarcosine, Potassium Aspartate, Magnesium Aspartate, Lavandula Angustifolia (Lavender) Flower/leaf Stem Extract, and Malonic Acid.

The Protective Composition

Suitable protective compositions include any composition capable of reducing skin damage, darkening, or dryness. In embodiments, protective compositions include sun block or sunscreen to filter out ultraviolet light rays. A wide variety of sunscreen actives are useful herein. The exact amount and type of sunscreen that is used depends on the level of photoprotection that is desired. Generally any agent offering protection against ultraviolet radiation by absorbing, scattering or reflecting the ultraviolet radiation may be used herein. The sunscreen agents used herein may offer protection against one or more of the following forms of solar radiation: UVA; UVB; UVC; visible light; and infrared radiation. Generally the sunprotection factor (SPF) of the final formulation varies between 2 and 30, although products with SPFs up to 100 may be formulated. The sunscreen used herein may offer chemical or physical photoprotection.

Sunscreens which may be used in accordance with the present invention include those selected from the group comprising amino benzoic acid and derivatives, such as para-amino benzoic acid (PABA), glyceryl-PABA (Lisadimate), Padimate O, Roxadimate; anthrinalates, including methylanthrynilate; benzophenones, including dioxyben-

zone, oxybenzone and sulisobenzone, 3-benzophenone (Uvinul M40) 4-N,N-dimethylaminobenzoic acid ester with 2,4-dihydroxybenzophenone; camphor derivatives including 3-(4-methylbenzylidene) camphor, 3-benzylidene camphor; cinnamates including DEA-p-methoxycinnamate, ethyl-hexyl p-methoxy cinnamate, octocrylene, octyl methoxy cinnamate (Parasol MCX); dibenzoyl methanes including butylmethoxydibenzoylmethane (Parsol 1789), salicylates including, homomenthyl salicylate, octyl salicylate, trolamine methyl salicylate; metal oxides including titanium dioxide, zinc oxide and iron oxide; 2-phenylbenzimidazole-5-sulfonic acid; 4,4-methoxy-t-butyldibenzoylmethane; and mixtures thereof.

In embodiments, suitable protective compositions include creams, such as moisturizers formulated to help control dryness. In embodiments, the protective composition includes at least one of the following compounds: ZnO; Vitamin A; Vitamin D; and combinations thereof. Optionally, an anti-parasitic product may also be applied for more severe cases, for example, for the control of Dermodex mites.

In embodiments, the anti-parasitic product includes an anti-parasitic compound (such as, for example, pediculicidal or mticidal compounds) that eradicate organisms (such as, for example, ectoparasites, e.g., demodex follicular mites, or endoparasites) that inhabit hair follicles and/or the pores of the skin. Any conventional anti-parasitic compound may be employed. Non-limiting examples of suitable pediculicidal agents include natural or other pyrethrins, pyrethroids, permethrin, lindane, malathion, carbaryl, ivermectin and combinations thereof. Suitable miticides are represented by propynyl sulfites, triazapentadienes, chlorinated aromatics and dinitrophenols. In embodiments, the anti-parasitic product may include a combination of benzyl benzoate, and salicylic acid, a combination effective in eradicating skin parasites. Products including anti-parasitic compounds may be particularly useful in regimens for patients having stage two, stage three, and stage four rosacea.

Additional Components

Depending upon the severity of the rosacea, it may be desirable to apply an anti-acne medication to the afflicted skin following the application of the previous compositions. Some examples of useful anti-acne medications include, but are not meant to be limited to, benzoyl peroxide, antibiotics, retinoids, and combinations thereof. In embodiments, compositions containing benzoyl peroxide may be applied to the afflicted area prior to application of the protective compound. This may further reduce the popular and pustular lesions. Suitable benzoyl peroxide compositions may contain, for example, from about one percent to about ten percent by weight benzoyl peroxide.

In other embodiments it may be desirable to apply a composition containing a retinoid to the afflicted area after application of the protective compound. The term retinoid is intended to embrace any compound that binds to or otherwise interacts with a retinoid receptor. Suitable retinoids include retinol, retinoic acid, retinyl palmitate, retinyl propionate, retinyl acetate, tretinoin, isotretinoin, motretinide, adapalene, tazarotene, azelaic acid, as well as synthetic retinoid mimetics.

Although not wishing to be bound by this disclosure, it is believed that tretinoin passes through the skin cell membranes to the nucleus wherein it binds to nuclear receptors and regulates transcription of genes that mediate the rate of cell division and turnover, cell differentiation, formulation of new healthy collagen, and the repair of elastin. As a result, skin can be made firmer by the collagen formation as well as more flexible from the repair of elastin.

Tretinoin also increases the formation of normal keratinocytes (cells making up about 90% of the epidermis) and fibroblasts (connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules), decreases melanocyte activity (which offers better resistance to external injury and inflammation) and is found to improve angiogenesis (the formation of new blood vessels that increase skin circulation).

In still other embodiments, it also may be desirable to apply a composition containing an antibiotic to the afflicted area after application of the protective compound. Any antibiotic known to have a beneficial effect upon the skin may be employed. In embodiments, the antibiotic used is clindamycin, tetracycline, erythromycin or combinations thereof. The antibiotic may be applied topically to the afflicted skin or administered in another manner, such as orally to the subject suffering from rosacea.

The various products applied in a regimen in accordance with the present disclosure can be in the form of solutions, emulsions (including microemulsions), suspensions, creams, lotions, gels, powders, or other typical solid or liquid compositions used for treatment of age related skin conditions. Such compositions may contain, in addition to the specific active(s) identified herein for each product, other ingredients typically used in such products, such as antimicrobials, moisturizers and hydration agents, penetration agents, preservatives, emulsifiers, natural or synthetic oils, solvents, surfactants, detergents, gelling agents, emollients, antioxidants, fragrances, fillers, thickeners, waxes, odor absorbers, dyestuffs, coloring agents, powders, viscosity-controlling agents and water, and optionally including anesthetics, anti-itch actives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humectants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

Polymetal Complex

The present disclosure also describes methods for treating skin afflicted with rosacea which include the step of applying a redness-reducing amount of a polymetal complex to at least a portion of the afflicted skin. In embodiments, the polymetal complex, e.g., Cu/Zn malonate is combined with a moisturizer and applied to the afflicted skin. The polymetal complex may be applied alone, following cleansing, or as a moisturizer. When used in the present regimens as a moisturizer, the polymetal complex improves capillary elasticity.

The polymetal complex can be the reaction product of a polyfunctional compound with two or more coordination elements. The preparation of reaction products of polyfunctional compounds with two or more coordination elements and compositions containing such reaction products are described. In embodiments, the resulting polymetal complex includes a first metal ion, a second metal ion that is different from the first metal ion and a central bridging unit linking the first and second metal ions, the central bridging unit being derived from a polyfunctional compound of the type described herein.

The polyfunctional compound can be any compound that contains at least two functional groups that may complex with metal cations in solution. Among the functional groups that may be present include carboxylic acid groups and amino groups. Suitable polyfunctional compounds include, but are not limited to polyfunctional acids, polyfunctional amines and amino acids. Other suitable polyfunctional compounds will be readily envisioned by those skilled in the art

reading the present disclosure. It should of course be understood that mixtures of polyfunctional compounds may be used.

Polyfunctional acids are primarily monomeric compositions having two or more carboxylic acid groups. Non-limiting examples of polyfunctional acids include maleic acid, fumaric acid, citraconic acid, itaconic acid, glutaconic acid, phthalic acid, isophthalic acid, terephthalic acid, cyclohexane dicarboxylic acid, citric acid, succinic acid, adipic acid, sebacic acid, azealic acid, malonic acid, dodecanedioic acid, 1,18-octadecanedioic acid, dimer acids (prepared from a mono-, di- or triunsaturated fatty acid, acid wax, acid anhydride grafted wax, or other suitable polycarboxylic acid reacting compound), alkenyl succinic acids (such as n-dodecenylsuccinic acid, docecylcucinic acid and octadecenylsuccinic acid). Polysaccharides having two or more carboxylic groups can be used as the polyfunctional acid compound. Thus, for example, hyaluronic acid may be used as the polyfunctional compound. The polyfunctional acid can be present in acidic form, anhydride form, salt form, or mixtures thereof. Any derivative of any polyfunctional acid can be used provided the derivative still contains two carboxylic acid groups. In embodiments, the polyfunctional acid chosen as the polyfunctional compound contains exactly two carboxylic acid groups.

Amino acids may also be used as the polyfunctional compound. Amino acids are known to those skilled in the art and include at least a carboxylic acid functionality and an amino functionality. In embodiments, the amino acid chosen as the polyfunctional compound contains two carboxylic acid groups. Suitable amino acids include naturally occurring amino acids and synthetic amino acids. Non-limiting examples of amino acids include, but are not limited to: aminopolycarboxylic acids (e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β-hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β,β-dimethylaspartic acid, γ-hydroxyglutamic acid, β,γ-dihydroxyglutamic acid, β-phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, β-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid); amino acid amides such as glutamine and asparagine; polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β-aminoalanine, γ-aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid; other basic amino acid residues such as histidine; diaminodicarboxylic acids such as α,α'-diaminosuccinic acid, α,α'-diaminoglutaric acid, α,α'-diaminoadipic acid, α,α'-diaminopimelic acid, α,α'-diamino-β-hydroxypimelic acid, α,α'-diaminosuberic acid, α,α'-diaminoazelaic acid, and α,α'-diaminosebacic acid; imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid; mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acids such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino-α-methyl-δ-hydroxyvaleric acid, α-amino-α-ethyl-ϵ-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, aaminodiisoamyacetic acid, α-methylaspartic acid, α-methylgiutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, tert-leucine, β-methyltryptophan and α-amino-β-ethyl-β-phenylpropionic acid; β-phenylserinyl; aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyieucine, β-hydroxynorleucine, β-hydroxynorvaline, and α-amino-β-hydroxystearic acid; α-Amino, α-, γ-, δ- or ϵ-hydroxy acids such as homoserine, γ-hydroxynorvaline, δ-hydroxynorvaline and epsilon-hydroxynorleucine residues; canavine and canaline; γ-hydroxyornithine; 2.hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid; α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine; other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine; phenylalanine, tryptophan and ring-substituted a amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, aaminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dicloro, o-, m- or p-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitrophenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthylalanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan; α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and α-Hydroxy and substituted α-hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine. glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β-hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid,β,β-dimethylaspartic acid, γ-hydroxyglutamic acid, β,γ-dihydroxyglutamic acid, β-phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid. Polyaminoacids may also be used provided they form complexes with the coordination elements employed.

The polyfunctional compound is reacted with two or more coordination elements. The coordination elements can be chosen from the elements listed in Groups IIIA to VIIIA, Groups IB to IIIB, of periods 4 and 5 and aluminum in Group IIIB, period 3 of The Periodic Table of the Elements. Suitable non-limiting examples of elements listed in group IB of The Periodic Table of Elements include copper, silver, and gold. Suitable non-limiting examples of coordination elements include aluminum, scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, gallium, yttrium, zirconium, niobium, molybdenum, technetium, ruthenium, rhodium, palladium, silver, cadmium, and indium. Tin may also be used. Those skilled in the art will readily envision suitable compounds for providing the coordination elements in solution. In embodiments, the coordination element is provided for the reaction as a basic salt that can participate in an acid-base reaction with a polyfunctional compound containing two carboxylic acid groups.

In embodiments, the polymetal complex is a copper-zinc malonate. Copper-zinc malonates may be one or more ionic compounds formed by joining one or more independent copper molecules or ions and one or more independent zinc molecules or ions to a central unit by ionic bonds. For

example, the copper-zinc malonate may be in the form of a trinuclear cation, where structurally independent copper and zinc hydrates are bridged by a central unit such as an octahedral diaquadimalonatocopper (II) unit. However, various coordination modes are possible depending on the source of the copper and zinc and synthesis conditions. In embodiments, the central unit malonate ion may be a multi-membered ring such as eight-membered ring, six-membered ring, and four-membered metalocycle for bridging or chelating functions between the copper and zinc constituents. Accordingly, the crystal structures of copper-zinc malonates can be very diverse, from ionic to three-dimensional polymers. In embodiments, the copper-zinc malonates can be found in several hydrate, and polymorphic forms. Suitable copper-zinc malonate forms in accordance with the present disclosure include any salt formed from the neutralization of malonic acid by one or more copper containing molecules and one or more zinc containing molecules. In embodiments, copper and zinc are provided for the reaction as basic salts that can participate in an acid-base reaction with the two carboxylic acid groups present in malonic acid. Illustrative examples include salt formed by the neutralization of malonic acid by cupric carbonate ($CuCO_3Cu(OH)_2$), and zinc carbonate ($3Zn(OH)_2.2ZnCO_3$) in an aqueous solution.

It has been discovered that the compositions which contain the polymetal complex are useful in causing varying levels of vasoconstriction. Such an effect may be useful in treating rosacea. Moreover, the vasoconstrictive effect of the present compositions decrease the rate at which the body is able to clear the composition by local blood supply, thereby allowing the composition to remain at the site of application longer which increases the rate and depth of tissue penetration of the composition. In embodiments, the compositions of the present application may be combined with other vasoconstrictive agents to further enhance the effect of the polymetal complex. In still other embodiments, the compositions of the present application may be combined with vasodilating agents thereby decreasing the effect of the polymetal complex.

In embodiments, the polymetal complex may be combined with numerous ingredients to form products that can be applied to the skin of a person afflicted with rosacea. Such products may include a dermatologically or pharmaceutically acceptable carrier, vehicle or medium, for example, a carrier, vehicle or medium that is compatible with the tissues to which they will be applied. The term "dermatologically or pharmaceutically acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with these tissues or for use in patients in general without undue toxicity, incompatibility, instability, allergic response, and the like. In embodiments, compositions in accordance with the present disclosure can contain any ingredient conventionally used in cosmetics and/or dermatology. In embodiments, active ingredients may be formulated to provide crystals in solution, as well as solid forms. Methods of making the polymetal complex and formulating topical compositions containing them are described, for example, in published patent applications US-2007-0191620-A1, US-2007-0203354-A1, US-2007-0184017-A1, US-2007-0190190-A1, US-2008-0081077-A1, the entire contents of which are all incorporated herein by this reference.

In embodiments, products containing a polymetal complex in accordance with the present disclosure as an active ingredient can be in the form of solutions, emulsions (including microemulsions), suspensions, creams, lotions, gels, powders, or other typical solid or liquid compositions used for treatment of age related skin conditions. Such compositions may contain, in addition to the reaction product in accordance with this disclosure, other ingredients typically used in such products, such as antimicrobials, moisturizers and hydration agents, penetration agents, preservatives, emulsifiers, natural or synthetic oils, solvents, surfactants, detergents, gelling agents, emollients, antioxidants, fragrances, fillers, thickeners, waxes, odor absorbers, dyestuffs, coloring agents, powders, viscosity-controlling agents and water, and optionally including anesthetics, anti-itch actives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humectants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

As an illustrative example, products can be formulated to contain copper-zinc malonate in amounts from about 0.001 to about 5% by weight of the total composition. In embodiments, products can be formulated to contain copper-zinc malonate in an amount from about 0.05 to about 1.0% by weight of the total composition. In other embodiments, the amount of copper-zinc malonate is from about 0.1 to about 0.5% by weight of the total composition. Here, the copper-zinc malonate present may be in a pharmaceutically acceptable salt form. Other active ingredients may be provided in the formulations at the same concentrations.

Table A below provides an illustrative embodiment of a suitable composition containing a polymetal complex in accordance with the present disclosure.

TABLE A

Ingredient	Decsription (function)	Amount
Water Phase		
Distilled Water	(solvent, humectant)	69.4940
PHENONIP	Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben, Propylparaben, Isobutylparaben (preservative)	0.8000
Propylene Glycol	(humectant)	1.5000
Glycerin	(humectant)	2.5000
Veegum Granules	Magnesium Aluminum Silicate (suspending agent)	0.4000
Keltrol CG	Xanthan Gum (viscosity building agent)	0.6000
Oil Phase		
Finsolv TPP	C_{12-15} Alkyl Benzoate; Dipropylene Glycol Dibenzoate, PPG - 15 Stearyl Ether Benzoate, 50%/35%/15%; 2.25%/1.575%/0.75% (emollient)	4.5000
GE Silicone SF 1214	Cyclopentasiloxane, Dimethicone, 80/20; 2.4%/0.6% (emollient)	3.0000
Gemseal 25	C_{13-15} Alkane (emollient)	3.0000
Pelemol OP	Ethylhexyl Palmitate (emollient)	3.0000
Lipomulse 165	Glyceryl Stearate, PEG-100 Stearate 2.475%/2.025% (emulsifier)	4.5000
Cetyl Alcohol	(thickener)	0.5000
Stearyl Alcohol	(thickener)	1.5000
GE Silicone 96-100	Dimethicone (emollient)	1.0000

TABLE A-continued

Ingredient	Decsription (function)	Amount
Abil Wax	Cetyl Dimethicone (emollient)	0.1000
Vitamin E Acetate	(vitamin)	0.0500
Engelhard Flamenco Satin Green P860	Mica, Titanium Dioxide, Iron Oxides (pigments)	0.0100
Kobo BPD 500	HDI/Trimethylol Hexyllactone Crosspolymer, Silica	0.0100
Presperse - Coverleaf AR-80	Talc, Titanium Dioxide, Alumina, Silica (pigments)	0.0010
Copper-Zinc Malonate	(active)	2.5000
Sepigel 305	Polyacrylamide, C_{13-14} Isoparaffin, Laureth - 7 (viscosifier/suspending agent)	1.0000
Extract Blend	Algae Extract, *Glycyrrhiza Clabra* Root Extract (antioxidants)	0.0100
Blueberry Fruit Extract	(antioxidants)	0.025
8% NaOH Solution	(ph adjusting agent)	QS
10% Malonic Acid Solution		QS

In embodiments, regimens for treatment of rosacea involve the sequential application of a series of products to the skin of a person afflicted with rosacea. The specific sequence of products applied in accordance with this disclosure will depend on the severity of the rosacea. The regimens for treating rosacea described herein may include the application of a composition containing a polymetal complex and may further include the application of one or more of the following: an antibiotic or antimicrobial cleanser, a protective composition, an anti-parasitic product and various combinations thereof. In embodiments, the cleanser is applied to at least a portion of the afflicted skin prior to the application of the composition containing a polymetal complex. In embodiments, the protective composition is applied to at least a portion of the afflicted skin following the application of a composition containing a polymetal complex.

In still other embodiments, at least three products may be used to treat the afflicted skin. The three products applied may be an antimicrobial or antibiotic cleanser, a composition containing a polymetal complex, and a protective composition. In embodiments, the composition containing a polymetal complex contains Cu/Zn malonate.

As the rosacea treatment regimens described herein require the sequential application of various components, it has also been found that kits greatly facilitate the user in performing the treatment regimen consistently. With respect to the composition containing metronidazole, the composition is currently a prescription medication that can be procured in addition to the kit or as a prescription kit. However, in the future if a composition containing metronidazole becomes an over-the-counter product, inclusion in a non-prescription kit is contemplated. One suitable kit for rosacea treatment includes the following:

Antimicrobial-containing cleanser
Anti-Redness Composition
Sunscreen with ZnO and vitamins A and D
Optionally one or more of:
Benzoyl Peroxide Composition
Retinoid Composition
Antibiotic Composition

In embodiments, the kit contains:

A cleanser
A composition containing a polymetal complex
A protective composition
Sunscreen with ZnO and vitamins A and D
Optionally one or more of:
Benzoyl Peroxide Composition
Retinoid Composition
Antibiotic Composition
composition containing metronidazole

In other embodiments, the kit contains:

A cleanser
A composition containing a polymetal complex
A composition containing metronidazole
An anti-redness composition
A protective composition

In yet other embodiments, the kit contains:

Antimicrobial containing cleanser
Product containing anti-parasitic compounds
Moisturizer with Cu/Zn malonate
Sunscreen with ZnO and vitamins A and D
Optionally one or more of:
Benzoyl Peroxide Composition
Retinoid Composition
Antibiotic Composition

An illustrative regimen in accordance with the present disclosure is as follows:

AM	PM
Gentle Cleanser	Gentle Cleanser
Metronidazole Gel 0.75%	Metronidazole Gel 0.75%
Anti-Redness Composition (Hydrating Complexion Corrector)	Anti-Redness Composition (Hydrating Complexion Corrector)
Skin Balancing Sun Protection SPF 30	

In embodiments, a regimen in accordance with the present disclosure is as follows:

AM	PM
Gentle Cleanser	Gentle Cleanser
Metronidazole Gel 0.75%	Metronidazole Gel 0.75%
Moisturizer with Cu/Zn malonate	Moisturizer with Cu/Zn malonate
Anti-Redness Composition (Hydrating Complexion Corrector)	Anti-Redness Composition (Hydrating Complexion Corrector)
Skin Balancing Sun Protection SPF 30	

Typically, kits are provided with instructions for care. For example, the instructions may direct that the various compositions of the pre-procedure treatment regimen be applied as follows:

Rosacea type	Product 1	Product 2	Product 3	Product 4	Product 5
Type 1 (mild)	cleanser	Moisturizer with Cu/Zn malonate	Sunscreen based on ZnO and Vitamin A&D		
Type 2 (moderate)	cleanser	Moisturizer with Cu/Zn malonate	Sunscreen based on ZnO and Vitamin A&D	Anti parasitic product 1% BPO lotion	Retinoic acid
Type 3 (severe)	cleanser	Moisturizer with Cu/Zn malonate	Sunscreen based on ZnO and Vitamin A&D Sunscreen	Anti parasitic product 1% BPO lotion	Oral minocycline or tetracycline antibiotic

The rosacea treatment regimen involves applying designated products in the smallest possible amount sufficient to cover at least a portion of the site afflicted with rosacea. In embodiments, the designated products may also be applied to the entire face of the patient even if only a small area of the face is afflicted with rosacea.

EXAMPLES

Example 1

An anti-redness composition suitable for use in the presently described regimen is prepared having the composition shown in Table B. The composition is prepared by combining the Water Phase ingredients in a reaction vessel with heating to 70 to 75° C. and stirring. The Oil Phase ingredients are combined in a separate reaction vessel with heating to 70-75° C. and stirring. The Oil Phase is then added to the Water Phase with continued stirring until a homogeneous dispersion is achieved. The Additional Ingredients are then added with stirring.

TABLE B

Ingredients	Percent	INCI Names	Functionality
Water Phase			
Distilled Water	54.08	Water	Solvent, Moisturizer
Phenonip	1.00	Phenoxyethanol, Methylparaben, Ethylparaben, Butylpraben, Propylparaben, Isobutylparaben	Preservative
Carbowax 300	2.25	PEG - 6	Humectant, solvent
Glycerin	0.50	Glycerin	Humectant, skin conditioner
Di-Propylene Glycol	2.25	Dipropylene Glycol	Humectant, solvent
Keltrol CG	0.25	Xanthan Gum	Suspending agent, thickener
Veegum	0.15	Magnesium Aluminum Silicate	Suspending agent, thickener
Oil Phase			
Pelemol OP	2.75	Ethylhexyl Palmitate	Emollient
Pelemol ICB	1.50	Isocetyl Behenate	Emollient
Cetiol LC	2.75	Coco-Caprylate/Caprate	Emollient
Permethyl 101A	4.50	Isohexadecane	Emollient
Gemseal 25	1.00	C13-15 Alkane	Emollient
Lipomulse 165	2.50	Glyceryl Stearate, PEG 100 Stearate	Emulsifier
Cetyl Alcohol	0.50	Cetyl Alcohol	Thickener, emulsion stabilizer
Stearyl Alcohol	1.50	Stearyl Alcohol	Thickener, emulsion stabilizer
GE Slicone 96-100	1.00	Dimethicone	Skin Protectant
Vitamin E Acetate	0.05	Tocopheryl Acetate	Anti-Oxidant
Titanium Dioxide MT-500B	5.00	Titanium Dioxide	Opacyfing and covering agent
Coverleaf AR 80	2.00	Talc, Titanium Dioxide, Alumina, Silica	Soft focus characteristic
Simulgel INS 100	2.00	Hydroxyethyl Acrylate/Sodium Acryloldimethyl Tauarte Copolymer, Isohexadecane, Polysorbate 60	Emulsifier, thickener
Additional Ingredients			
Soft Tex Yellow Iron Oxide C337773	0.03	Iron Oxide	Tinting/coloring ingredient
Soft Tex Red Iron Oxide C337775	0.03	Iron Oxide	Tinting/coloring ingredient
Soft Tex Black Iron Oxide C337734	0.02	Iron Oxide	Tinting/coloring ingredient
Water	3.00	Water	Solvent, moisturizer

Example 2

A protective composition suitable for use in the presently described regimen is prepared having the composition shown in Table C. The composition is prepared by combining the Water Phase ingredients in a reaction vessel with heating to 70-75° C. and stirring. The oil phase ingredients are combined in a separate reaction vessel with heating to 70-75° C. and stirring. The oil phase is then added to the water phase with continued stirring until a homogenous dispersion is achieved. The additional ingredients are then added with stirring.

TABLE C

Ingredient		Percent	INCI Name	Functionality
Aqueous Phase				
Water		50.0550	Water	Solvent, moisturizer
Glycerin		0.5000	Glycerin	Humectant, skin conditioner
Dipropylene Glycol		10.0000	Dipropylene Glycol	Humectant, solvent
CARBOWAX 300 ®		3.0000	PEG-6	Humectant, solvent
PHENONIP ®		1.0000	Phenoxyethanol, Methylparaben, Propylparaben, Ethylparaben, Butylparaben, Isobutylparaben	Preservative
Oil Phase				
MONTONOV ® 82		2.0000	Cetearyl Alcohol, Cocoa Glucoside	
PERMETHYL 101A ®		0.3000	Isohexadecane	Emollient
KOBO TNP5OzSI	11.28% Zinc Oxide (47%)	24.0000	C12-15 Alkyl Benzoate, Zinc Oxide, Polyhydroxystearic Acid, Triethoxycaprylsilane	Sunscreen
Vitamin E Acetate		0.0500	Tocopheryl Acetate	Anti-Oxidant
Z COTE ®	4.5% Zinc oxide	4.5000	Zinc Oxide	Sunscreen, Skin Protectant
Micro Titanium Dioxide MT 500B		1.8000	Titanium Dioxide	Sunscreen
Kobo TNP40VTTS	0.32% Titanium Dioxide (32%)	1.0000	C12-15 Alkyl Benzoate, Titanium Dioxide, Alumina, Polyhydroxystearic Acid, Isopropyl Titanium Triisostearatel Triethoxycaprylysilane Crosspolymer	Sunscreen
Additional Ingredients				
Flamenco satin Green 860 M		0.2500	Mica, Titanium Dioxide, Iron Oxides	Helps to diminish skin redness
Soft Tex Yellow Iron Oxide C337773		0.0200	Iron Oxide	Tinting masstone
Soft Tex Red Iron Oxide C337775		0.0150	Iron Oxide	Tinting masstone
Soft Tex Black Iron Oxide C337734		0.0100	Iron Oxide	Tinting masstone
Sepinov EMT 10		1.5000	Hydroxyethylacrylate/Sodium Acrylolyldimethyl Taurate	Emulsifier

Example 3

Another protective composition suitable for use in the presently described regimen is prepared having the composition shown in Table D. The composition is prepared by combining the Water Phase ingredients in a reaction vessel with heating to 70-75° C. and stirring. The oil phase is then added to the water phase with continued stirring until a homogeneous dispersion is achieved.

TABLE D

Ingredient		Percent	INC Name	Functionality
Aqueous Phase				
Water		50.0550	Water	Solvent, moisturizer
Glycerin		0.5000	Glycerin	Humectant, skin conditioner
Dipropylene Glycol		10.0000	Dipropylene Glycol	Humectant, solvent
CARBOWAX 300 ®		3.0000	PEG-6	Humectant, solvent
PHENONIP ®		1.0000	Phenoxyethanol, Methylparaben, Propypylparaben, Ethylparaben, Butylparaben, Isobutylparaben	Preservative
Oil Phase				
MONTONOV ® 82		2.0000	Cetearyl Alcohol, Cocoa Glucoside	
PERMETHYL 101A ®		0.3000	Isohexadecane	Emollient
KOBO TNP5OzSI	11.28% Zinc Oxide (47%)	24.0000	C12-15 Alkyl Benzoate, Zinc Oxide, Polyhydroxystearic Acid, Triethoxycaprylsilane	Sunscreen
Vitamin E Acetate		0.0500	Tocopheryl Acetate	Anti-oxidant
Z COTE ®	4.5% Zinc oxide	4.5000	Zinc Oxide	Sunscreen, Skin Protectant
Micro Titanium Dioxide MT 500B		1.8000	Titanium Dioxide	Sunscreen

TABLE D-continued

Ingredient		Percent	INC Name	Functionality
Kobo TNP40VTTS	0.32% Titanium Dioxide (32%)	1.0000	C12-15 Alkyl Benzoate, Titanium Dioxide, Alumina, Polyhydroxystearic Acid, Isopropyl Titanium Triisostearatel Triethoxycaprylysilane Crosspolymer	Sunscreen
Additional Ingredients				
Flamenco satin Green 860 M		0.2500	Mica, Titanium Dioxide, Iron Oxides	Helps to diminish skin redness
Soft tex Yellow Iron Oxide C337773		0.0200	Iron Oxides	Tinting masstone
Soft tex Red Iron Oxide C337775		0.0150	Iron Oxides	Tinting masstone
Soft tex Black Iron Oxide C337734		0.0100	Iron Oxides	Tinting masstone
Sepinov EMT 10		1.5000	Hydroxyethylacrylate/Sodium Acrylolyldimethyl Taurate	Emulsifier

Example 4

An additional anti-redness composition suitable for use in the presently described regimen is prepared having the composition shown in Table E. The composition is prepared by combining the Water Phase ingredients in a reaction vessel with heating to 70-75° C. and stirring. The Oil Phase is then added to the Water Phase with continued stirring until a homogeneous dispersion is achieved. The Additional Ingredients are then added with stirring.

TABLE E

Ingredients	Percent	INCI Names	Functionality
Water Phase			
Distilled Water	54.08	Water	Solvent, Moisturizer
Phenonip	1.00	Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben, Propylparaben, Isobutylparaben	Preservative
Carbowax 300	2.25	PEG-6	Humectant, solvent
Glycerin	0.50	Glycerin	Humectant, skin conditioner
Di-Propylene Glycol	2.25	Dipropylene Glycol	Humectant, solvent
Keltrol CG	0.25	Xanthan Gum	Suspending agent, thickener
Veegum	0.15	Magnesium Aluminurn Silicate	Suspending agent, thickener
Oil Phase			
Pelemol OP	2.75	Ethylhexyl Palmitate	Emollient
Pelemol ICB	1.50	Isocetyl Behenate	Emollient
Cetiol LC	2.75	Coco-Caprylate/Caprate	Emollient
Permethyl 101A	4.50	Isohexadecane	Emollient
Gemseal 25	1.00	C13-15 Alkane	Emollient
Lipomulse 165	2.50	Glyceryl Stearate, PEG 100 Stearate	Emulsifier
Cetyl Alcohol	0.50	Cetyl Alcohol	Thickener, emulsion stabilizer
Stearyl Alcohol	1.50	Stearyl Alcohol	Thickener, emulsion stabilizer
GE Slicone 96-100	1.00	Dimethicone	Skin Protectant
Vitamin E Acetate	0.05	Tocopheryl Acetate	Anti-Oxidant
Titanium Dioxide MT-500B	5.00	Titanium Dioxide	Opacyfing and covering agent
Coverleaf AR 80	2.00	Talc, Titanium Dioxide, Alumina, Silica	Soft focus characteristic
Simulgel INS 100	2.00	Hydroxyethyl Acrylate/Sodium Acryloldimethyl Tauarte Copolymer, Isohexadecane, Polysorbate 60	Emulsifier, thickener
Additional Ingredients			
Soft Tex Yellow Iron Oxide C337773	0.03	Iron Oxide	Tinting/coloring ingredient
Soft Tex Red Iron Oxide C337775	0.03	Iron Oxide	Tinting/coloring ingredient
Soft Tex Black Iron Oxide C337734	0.02	Iron Oxide	Tinting/coloring ingredient
Water	3.00	Water	Solvent, moisturizer
Activera 1-200A	0.50	*Aloe Barbadensis* Leaf juice	Soothing, calming agent
Hydrolyzed Oat Protein 6-055 LC	0.50	Hydrolyzed Oat Protein, water, Glycerin, Phenoxyethanol	Soothing, conditioning agent
Bisabolol (lipo)	0.20	Bisabolol	Anti-inflammatory, Anti-irritant, anti-microbial
Allantoin	0.50	Allantoin	Skin Protectant
Oat Beta Glucan 6-070 L	0.25	*Avena Sativa* (Oat) Beta Glucan, *Avena Sativa* (Oat) Kernel Extract, Phenoxyethanol, Water	Soothing, conditioning
Licorice ECO	0.10	Glycerin, wate, Glycyrrhiza Glabra root extract	Anti-inflammatory, Energized immune system, Anti-microbial, anti-oxidant.
Gorgonian Extract PTG	0.10	Pentylene Glycol, Sea Whip Extract	Anti-inflammatory
Flamenco Satin Green 860M	0.25	Mica, Titanium Dioxide, Iron Oxides	Helps to diminish appearance of red skin
Bacocalmine	2.00	*Bacopa Monniera* Extract, Water. PEG 8, Hydroxycellulose	Anti-irritation & anti-inflammatory

TABLE E-continued

Ingredients	Percent	INCI Names	Functionality
Phytotonine	2.00	Propylene Glycol, *Arnica Montana* (Flower) Extract, *Cupressus Sempervirens* (Seed) Extract, *Polygontum Multiflorum* Extract	Increases microcirculation and strengthens vein walls
Sepicalm S	2.00	Sodium Cocoyl Amino Acid, Sarcosine, Potassium Aspartate, Magnesium Aspartate	Against UV stress, mechanical aggressions, Against inflammation and soothes skin
Lavender Extract H0539	1.00	*Lavandula Angustifolia* (Lavender) Flower/leaf Stem extract	Antispetic and anti-inflammatory
5% NaOH solution		Water, Sodium Hydroxide	Buffering Agent
5% Malonic Acid		Water, Malonic Acid	Buffering Agent

Example 5

A 25-day, half-face, randomized study was conducted to determine if the use of a regimen in accordance with the present disclosure decreases the red/irritated skin of Rosacea subjects when compared to untreated skin. Approximately 10 subjects participated in the study. To facilitate enrollment, the qualification visit took place no sooner than 3 days prior to the start of the study. Potential subjects presented with red/irritated skin associated with Rosacea as determined by a Board-Certified Dermatologist during the qualification visit. Subjects with a global assessment score of 4 or greater (using a 10-point scale) with an equal value on the right and left side of the face and who meet the inclusion/exclusion criteria were enrolled. Each subject was required to respond to a baseline questionnaire prior to treatment at Day 0 (baseline). Global tolerability assessments were conduct by a trained evaluator pre- and post treatment during visits Day 0-4, 11 and 18. Tolerability assessments were conducted by a Board-Certified Dermatologist pre- and post-application on Day 25 (final visit). Subjects returned to the testing facility on Days 1-4, and the same procedures were followed as for Day 0. A series of photographs were taken of the right and left side of the face using the VISIA-CR® Image System (Canfield Scientific, Fairfield, N.J.). At all visits to the testing facility, the subjects applied products under the direction and supervision of the technician. The subjects made all PM applications at home, and responded to a questionnaire after the PM application. According to a randomization scheme, subjects were assigned the test products so that odd-numbered subjects applied the test products to the right side of the face, and the left side remained untreated. Even-numbered subjects applied the test products to the left side of the face while the right side of the face remained untreated. Subjects were given daily use instructions and a daily diary to record time of usage and any other safety related comments.

Subjects washed their faces only with the provided cleanser as instructed. Additionally, subjects came to the testing clinic without applying any cosmetic products to the face including moisturizers or facial powder. Ten (10) subjects were enrolled in the study based on the following criteria:

Inclusion Criteria

1. Male/Female 20-68 years of age. Fitzpatrick Skin Type I-III.
2. Moderate to severe (grades 4-9 on 10-point scale) redness/irritation associated with Rosacea uniformly distributed across the right and left side of the face (between and across cheeks). Subjects with papules/pustules preferred.
3. Subjects willing and able to sign the Informed Consent Form, to follow the study directions and to remain in the test facility for approximately 60 minutes at all scheduled visits to the clinic,
4. Female subjects willing to have a urine pregnancy test if not surgically sterile or post-menopausal at least 5 years at screening (baseline) and study end or withdrawal from the study.
5. Subjects free of cuts, burns, scratches or any other condition on the face that, in the opinion of the investigator, may interfere with the proper conduct of the study.
6. Subjects willing to leave ½ side of the face untreated for the entire study.
7. Subjects willing to refrain from excessive sun exposure and refrain from using tanning booths during the entire course of the study.

Exclusion Criteria

1. If female of childbearing potential: Pregnant or lactating as determined by urine pregnancy test if not surgically sterile or post-menopausal at least 5 years.
2. Allergy to benzoyl peroxide or salicylic acid.
3. Any facial skin disease, which can interfere with study results.
4. Sunburn/tan on the face.
5. Make-up on forehead/cheeks.
6. Use of the following medications within the described period (Note: topical refers to facial area):
   A) Medicated facial cleansers, including antibacterial soaps
   —1 week
   B) Topical AHAs and anti-acne medications (BPO, retinoids, antibiotics)—2 weeks
   C) Systemic antibiotics and investigational drugs
   —4 weeks
   D) Participation in a clinical study with OTC or RX drug on the face
   —4 weeks
7. Concurrent use of other medicated products on the face.
8. Concurrent participation in another clinical study.
9. History of cancer on the face.
10. Subjects with other abnormal clinical findings or systemic condition or uncontrolled
    disease, which the Investigator feels, may put the subject at undue risk or may interfere
    with the study results.
11. Subjects with blood disorders.
12. Subjects taking Anticoagulants.
13. Subjects taking Disulfiram

The study formulations are:

Gentle cleanser commercially availableforrn Obagi Medical Products, Long Beach Calif., USA under the tradename NU DERM® Gentle Cleanser

The anti-redness composition of Example 2

The protective composition of Example 1

Metronidazole Topical Gel USP 0.75%

There were a total of compositions used in the study. Each subject received a cleanser, protective composition and anti-redness treatment to be applied to the right or left side of the face according to the randomization scheme. The opposite side of the face remained untreated. Treatment was randomized between the right and left side of the face for odd and even-numbered subjects. The randomization scheme showed which treatment was assigned to each side of the face.

Prior to any application at the testing facility on Day 0 (baseline), the following procedures will be followed in the AM:

Baseline Photographs (VISIA CR® IMAGING SYSTEM) PHOTO #1

Baseline Subject Questionnaire

Baseline Global Assessment By A Trained Evaluator

Products were then applied according to the following procedure:

A.M. Treatment

1. A pea-sized amount of NU DERM Gentle Cleanser is dispensed, rubbed on wet hands and applied to full face and cleansed thoroughly, and rinsed with tepid water with technician supervision.

2. Post-wash photographs (VISIA CR® Imaging System) were taken immediately following wash.

3. Two pumps (approximately 1 ml) of the anti-redness composition of Example 4 were applied to one side of the face as instructed.

4. Two pumps (approximately 1 ml) of the protective composition of Example 3 were applied to one side of the face as instructed.

5. Immediately following application of previous two products, another photo was taken.

6. After waiting 10-30 minutes to determine when erythema subsided, another photo was taken.

7. A trained evaluator made an assessment of tolerability of the treatment.

P.M. Treatment at Home Prior to Bedtime

1. A pea-sized amount of NU DERM Gentle Cleanser is dispensed, rubbed on wet hands and applied to full face and cleansed thoroughly, and rinsed with tepid water.

2. 0.5 mL of Metronidazole (0.5 mL syringe delivery) was applied to one side of the face as instructed.

3. Two pumps (approximately 1 ml) of the anti-redness composition of Example 4 were applied to one side of the face as instructed.

Metronidazole was supplied to the subjects in pre-filled syringes at each scheduled visit, and each syringe delivered 0.5 mL of product (Metronidazole Topical Gel).

After applications, the subjects were given their assigned product with use instructions and a daily diary to record their daily usage and any safety related comments they may have. Subjects were also be given a questionnaire to be completed following their PM application just prior to bedtime. Subjects returned all completed questionnaires at the next scheduled visit. Photographs will be taken at the following time points at the Day 0 (baseline visit).

Baseline (photo #1)

Immediately post-wash (photo #2)

Post-treatment of both product applications (photo #3)

10-30 minutes post-treatment (photo #4)

Photographs were taken immediately post-wash and post-application of products at all other visits.

The subjects avoided any other medicated formulations on the face (including cleansers), and used only the products supplied to them during the study. Subjects were instructed not introduce any new facial cosmetics, soaps, shampoos, creams, lotions, etc. while on this study. Subjects were permitted to use their daily cosmetics (lipstick, eye makeup, foundation) during the study. However, subjects presented themselves to the clinic with nothing applied to their face at scheduled visits.

Irritation Evaluation

A trained evaluator assessed (global assessment) the right and left side of the face of each subject at all visits. The Board-Certified Dermatologist conducted the global tolerability assessments pre- and post-application of the test regimen on the final day of the study. Tolerability assessments were conducted according to the scales below.

Scale for Scoring Redness/Irritation

0=No irritation present

1-3=Mild irritation present

4-6=Moderate irritation present

7-9=Severe irritation present

Scale for Sensory Evaluation	
(stinging [S]), burning [B])	(itching [I])
0 = None—no stinging/burning	0 = No itching
1-3 = Mild—light warm, tingling sensation, not really bothersome	1-3 = Mild—occasional, slight itching
4-6 = Moderate—definite warmth, tingling sensation, that is somewhat bothersome	4-6 = Moderate—constant or intermittent itching that is somewhat bothersome
7-9 = Severe—hot tingling sensation which is disturbing normal activity	7-9 = Severe—bothersome itching which is disturbing normal activity

Photographic images taken using the VISIA CR® (Canfield Scientific) will be analyzed using Image PRO® software to determine changes (if any) in the a* value (white to red). An increase in the a* value indicates an increase in erythema.

All data points collected after Days 0-4, 11, 18, and 25 were compared to the baseline for each subject for differences between the time points and control. The average results for all subjects of the post-wash comparisons are presented in Table F. The data in Table F shows that at day zero, the negative 0.71 value indicates that the untreated side of face in study was redder initially than the side of the face that was not part of the study. This is simply a result of the randomness of the study. Between day 0 and day 4, the treated side of the face became the less red side as a result of the treatment.

TABLE F

Day	a* values
1	-0.71
4	.14
11	.36
18	.25
25	.61

The summation of the difference was analyzed using the Wilcoxon Signed-Rank Test. A response was considered statistically significantly different from baseline when the p-value is <0.05.

The tested regimen resulted in a marked reduction in redness. As shown in Table F, after washing, the redness of

the treated side was reduced significantly compared to the control side of the face. This reduction was greater than the redness reduction expected from Metrogel alone, especially since the clinical application for Metrogel is resolution of lesions, not the reduction of redness.

While several embodiments of the disclosure have been described, it is not intended that the disclosure be limited thereto, as it is intended that the disclosure be as broad in scope as the art will allow and that the specification be read likewise. Therefore, the above description should not be construed as limiting, but merely as exemplifications of embodiments.

What is claimed is:

1. A method of promoting vasoconstriction of an area of skin afflicted with rosacea, consisting essentially of:

cleansing the area of skin afflicted with rosacea;

applying a redness reducing amount of a composition containing a Cu/Zn malonate complex to the afflicted area;

applying a composition containing metronidazole to the afflicted area;

applying a protective composition to the afflicted area that has been cleansed and treated with the composition containing the Cu/Zn malonate complex and the composition containing metronidazole, which protective composition optionally further includes a sunscreen;

wherein the composition containing the Cu/Zn malonate complex optionally further includes a moisturizer, and the cleansing step optionally includes cleaning the area of skin afflicted with rosacea with an antimicrobial cleanser, and

wherein the method optionally further consists essentially of applying an anti-parasitic product and/or an anti-acne medication to the area of skin afflicted with rosacea after the protective composition is applied,

thereby promoting vasoconstriction of the area of skin afflicted with rosacea.

2. The method of claim **1**, wherein the antimicrobial cleanser is selected from the group consisting of chlorhexidine gluconate, triclosan, zinc pyrithione, clindamycin phosphate, sodium sulphacetamide and combinations thereof.

3. The method of claim **1**, wherein the sunscreen comprises a compound selected from the group consisting of ZnO, Vitamin A, Vitamin D and combinations thereof.

4. The method of claim **1**, wherein the anti-parasitic product includes a compound selected from the group consisting of benzyl benzoate, salicylic acid and combinations thereof.

5. The method of claim **1**, wherein the anti-acne medication is selected from the group consisting of benzoyl peroxide, retinoids, tetracycline, clindamycin, erythromycin, and combinations thereof.

6. The method of claim **1**, wherein the composition containing metronidazole is formulated as a gel preparation.

7. The method of claim **1**, wherein the composition containing metronidazole contains from 0.001% to 5% metronidazole by weight of the composition.

* * * * *